Neuropharmacological Therapy of the Neuroendocrine Carcinoid Syndrome: Report of Two Cases

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ABSTRACT

We discuss two cases of patients affected by the carcinoid syndrome who showed adrenal over neural sympathetic predominance and a TH-2 immunological profile. Both received neuropharmacological therapy addressed to reverting this autonomic nervous system imbalance. Clinical, autonomic nervous system and immunological improvements were registered as of the first 4-week post-treatment period. No relapses have been recorded up to the present (4 and 3 years later, respectively). The neuropharmacological therapy addressed to enhancing central nervous system-noradrenergic activity, which is able to revert adrenal over neural sympathetic predominance, seems to be a valuable tool in treating patients affected by carcinoid syndrome. The fact that patients affected by carcinoid presented common neuroautonomic disorders led us to prescribe the neuropharmacological therapy addressed to revert that abnormal profile. Although we have assessed several of the above-mentioned patients, we refer here only to these two well-investigated, treated, and followed-up patients.

INTRODUCTION

Our laboratory of neurochemistry and immunology has investigated some 25,000 normal and diseased subjects. Circulating neurotransmitters and immunological parameters are routinely assessed before and after neuropharmacological manipulations through several stress tests, such as the supine-resting, one-minute orthostasis, and five-minute exercise challenges. The results of these tests enable us to evaluate the contribution of the two branches of the peripheral autonomic sympathetic system: neural and adrenal.[1-3] However, because

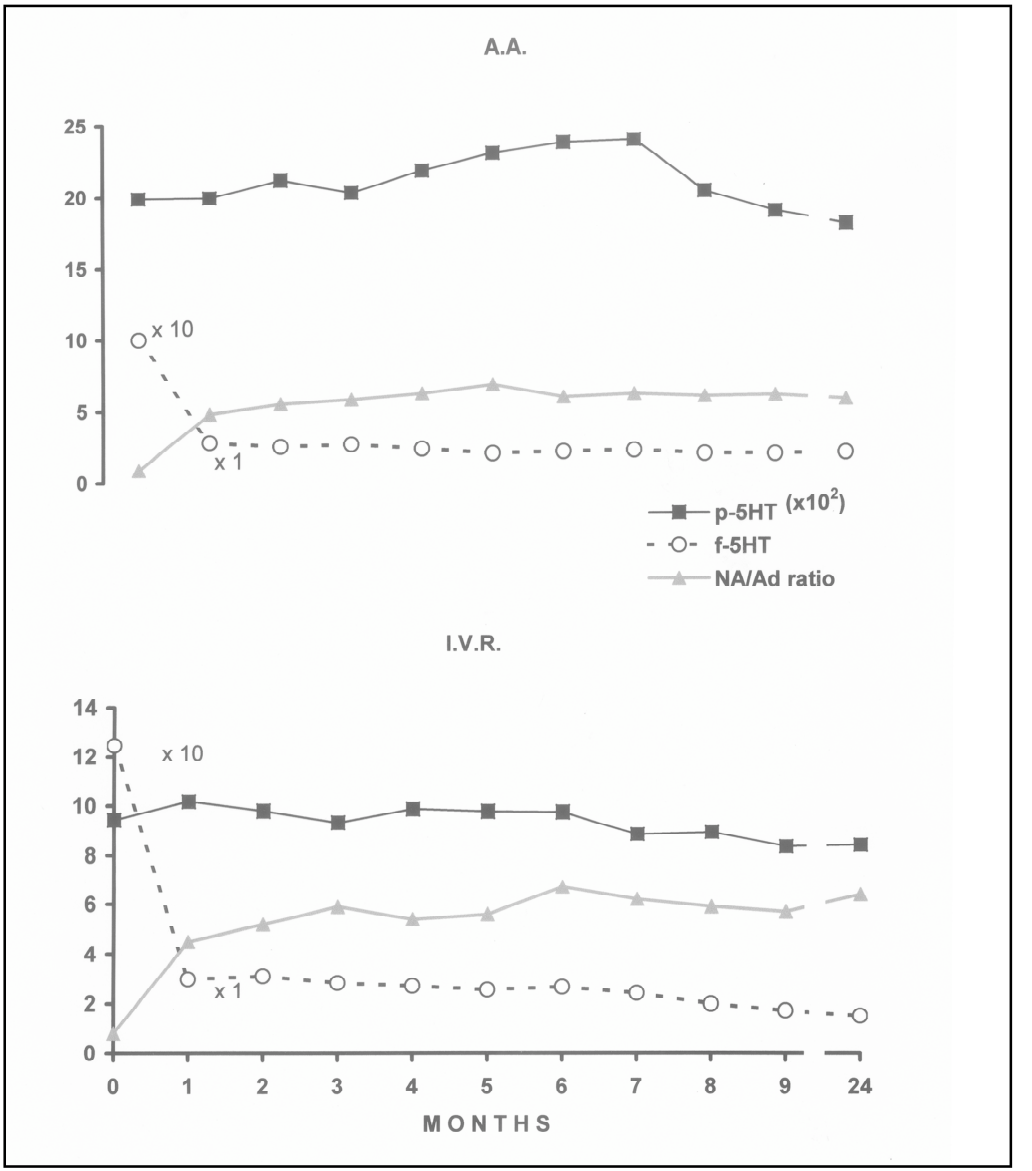

Figure. Changes registered throughout the neuropharmacological therapy in two carcinoid patients. Maximal improvement was reached since the first month of therapy, and was paralleled by normalization of f-5HT plasma values. No further relapses were registered. NA indicates noradrenaline; Ad, adrenaline; p-5HT, platelet serotonin; and f-5HT, plasma serotonin. (f-5HT x 10 at pre-treatment period, only).

plasma acetylcholine levels are not detectable at peripheral circulation, we employ indirect evidence concerning the parasympathetic system activity through the assessment of circulating serotonin. This indolamine circulating pool is integrated by the addition of platelet- (p-5HT) and plasma- (f-5HT) serotonin. Normal f-5HT/p-5HT ratio is 0.5% to 2%. This ratio increases because hyperparasympathetic activity (acetylcholine [ACh]) interferes with platelet uptake[4] and hyperadrenergic activity secondary to platelet aggregation.[5] In addition to

the above, the measurement of plasma tryptophan reflects central nervous system (CNS) serotonergic activity.[6] Assessment of the immune profile is carried out through the evaluation of the usual immunological parameters which might help to design the profile according with the TH-1 versus TH-2 paradigm.[7,8]

CASE REPORTS

Case One

A. A. is a 46-year-old man who underwent surgical resection of the terminal ileum (59 cm) and appendix because of a big carcinoid tumor. Ganglional and hepatic metastases were detected. He rejected chemotherapy and was referred to our department on February 2, 2000.

An assessment of circulating neurotransmitters revealed high levels of catecholamines: noradrenaline (NA), adrenaline (Ad) and dopamine (DA); plus raised levels of indolamines: intraplatelet serotonin (p-5HT) + free serotonin in the plasma (f-5HT). Plasma levels of tryptophan, considered the hallmark of CNS serotonergic activity, were lower than normal. Although the sum of NA and Ad was greater than normal, the NA/Ad ratio was very low (< 1) at supine-resting condition. This ratio did not increase but rather decreased at one-minute orthostasis. As this abnormal response is a trustworthy index of poor neural sympathetic release, such raised levels of circulating catecholamines necessarily arise from the adrenal glands. It should be remembered that sympathetic nerves release 90% of NA and 10% of DA. Conversely, adrenal glands secrete 80% of Ad and 20% of NA and DA. Furthermore, considering that neural sympathetic but not adrenal sympathetic response would normally occur at one-minute orthostasis,[9] maximal reduction of the NA/Ad ratio observed in this patient reflects the absolute predominance of adrenal over neural sympathetic activity.[3] With respect to the above, it should be pointed out that whereas neural sympathetic release depends on NA neurons located at the pontine locus coeruleus nucleus (LC), the adrenal glands are ruled by Ad-C1 medullary neurons located at the rostral ventrolateral medulla. These two CNS sympathetic systems can function in association or dissociation,[10] in accordance with physiological requirements. However, the Ad-C1 medullary system is responsible for peripheral sympathetic activity when the LC-NA nucleus becomes exhausted, as occurs during stressful situations.[3]

Both platelet serotonin (p-5HT) and plasma serotonin (f-5HT) levels were very high. Plasma tryptophan showed lower than normal values, indicating poor CNS serotonergic activity.[1] Immunological investigations showed positive antinuclear autoantibodies (ANA) (++), plus very low NK cell cytotoxicity against K562 target cells (23%), raised IgG, and IgE plasma levels. Summarizing, the above results are consistent with the postulation of a deficit in neural sympathetic activity by NA neurons located at the LC-NA neurons, and an excess adrenal (Ad) gland sympathetic activity triggered by Ad-C1 medullary nuclei.[1] In light of this, a neuropharmacological therapy addressed to enhancing both CNS-NA and CNS-5HT activities was administered: doxepin (25 mg once daily) plus 5-OH-tryptophan (25 mg three times daily). Doxepin is an inhibitor of NA uptake (60%) and an inhibitor of 5-HT-uptake (40%), while 5-OH-tryptophan is a serotonin precursor that crosses the blood brain barrier easily.[11] Further, considering that circulating serotonin arises from enterochromaffin cells triggered by parasympathetic drive,[12] 7.5 mg of propantheline was administered before meals. This nicotine-receptor antagonist does not cross the blood brain barrier; it interrupts the

pre- to post-synaptic connection at the parasympathetic ganglia. Finally, a half tablet (0.075 mg) of oral clonidine was given before bed. This alpha 2-agonist crosses the blood brain barrier and bridles the Ad-C1 medullary nuclei responsible for adrenal gland secretion.[13] Progressive and significant improvement was obtained and sustained. The treatment covered three months, followed by two weeks of rest, after which it was restarted. Circulating neurotransmitters were controlled every 4 weeks. Parallel clinical and ANS improvements were observed. Increases of the NA/Ad ratio and tryptophan values were seen as of the first 4-week control. Platelet serotonin values remained greater than normal (Figure). Free-serotonin (f-5HT) showed significant decrease throughout the treatment. NK cell activity rose from 23% to 35%. This patient showed autonomic, immunological, and clinical normalization after the first three months of therapy. The improvement persists up to the present (December 2004). No metastases were detected (CAT scan).

Case Two

I.V.R. is a 43-year-old woman who was referred to our institute suffering from a neuroendocrine carcinoid disease, polipoid tumors located at small intestinal level were diagnosed when she was submitted to surgery for uterine fibromatosis and endomethriosis. She rejected chemotherapy. On entering our institute in September 17, 2001, she was exhaustively evaluated, having presented with flushing, tachycardia, and many other symptoms despite undergoing somatostatin therapy. The ANS investigation was evaluated throughout the supine-resting, orthostasis, and moderate exercise test, which showed greatly raised circulating catecholamine levels (NA, Ad, DA). However, not only NA, but Ad rose at one-minute orthostasis and increased during the 5-minute exercise period. NA/Ad ratio was very low at supine-resting state, and far from rising, fell during the two other periods (Figure). Diastolic blood pressure (DBP) showed a decrease rather than an increase, at one-minute orthostasis test. This DBP fall is attributed to the inhibition of NA release from sympathetic terminals exerted by prior release of DA from the DA pool there.[14] Finally, although both p-5HT and f-5HT were greatly increased, and tryptophan plasma values were lower than normal, immunological investigation showed a decreased CD4/CD8 ratio (0.9), positive antinuclear antibodies (+), and lower than normal NK cell activity (21%). This patient received similar therapy to that given to patient A.A. Clinical improvement was so quick that after the first 4-week period, NA/Ad ratio was normal; although p-5HT values remained high, f-5HT dropped to normal values. Immunological parameters also showed normalization. NK cell activity rose from 21% to 32%. The patient has remained free of symptoms up to the present (December 2004). All neurochemical and immunological parameters were found normal, also.

DISCUSSION

Two carcinoid patients, presenting adrenal over neural sympathetic predominance plus raised levels of circulating platelet serotonin (p-5HT) and plasma serotonin (f-5HT), as well as TH-2 immunological profile, were treated and improved by neuropharmacological therapy addressed to reverting adrenal over neural sympathetic predominance. This finding obliges us to think that both neuroautonomic and immunological disorders should be included among the pathophysiological mechanisms underlying this disease (TH-2 profile). This inference is reinforced by the finding that all clinical, ANS, and immunological improvements were triggered by neu-

ropharmacological manipulations similar to those used to revert AD over NA predominance.

The raised circulating serotonin level found in both patients agrees with the enterochromaffin-cell overactivity always present in this disease. Further, the fact that platelet serotonin (p-5HT) remained elevated, whereas the plasma serotonin (f-5HT) was normalized in these two carcinoid patients after clinical improvement, suggests that although their enterochromaffin cells remained overactive, the symptoms were related to the raised f-5HT plasma levels. Both the physiologic disorders and their clinical symptoms were paralleled by adrenal over neural sympathetic predominance periods. This phenomenon may be associated with the maximal ability of the neural sympathetic system to annul the parasympathetic drive that is responsible for enterochromaffin cell secretion and for increased f-5HT levels. This phenomenon would operate not only at the GI level, but at the metastatic extra-intestinal nodes. Circulating serotonin arises from enterochromaffin cells that release 5HT in response to parasympathetic drive.[15] Although most 5HT is secreted into the intestinal lumen, a fraction reaches portal circulation. Serotonin that escapes through liver and lungs uptake is trapped by platelets.[15] However, some fraction of serotonin always remains free in the plasma (f-5HT). The normal f-5HT/p-5HT circulating ratio is about 0.5% to 1%. This ratio increases during platelet aggregation[5] and deficit of platelet uptake. Platelet uptake is interfered by both circulating acetylcholine[4] (hyperparasympathetic activity) and circulating DA.[16] The former occurs during excessive parasympathetic drive. The increase of f-5HT registered in these circumstances may be exacerbated because the indolamine excites $5HT_3$ and $5HT_4$ receptors located at the medullary area postrema (outside the blood brain barrier), which is connected to the motor vagal complex.[17] This fact results in a further increase of the peripheral parasympathetic drive discharge over the enterochromaffin cells (Bezold-Harisch reflex). Such mechanisms may explain the hyper-serotonergic storm occurring in carcinoid patients.

The enhancement of NK-cell cytotoxicity, as well as the shifting of TH-2 to TH-1 immunological profile, triggered by the neuropharmacological therapy prescribed to these two carcinoid patients, merits special mention. In 1987, we found that neuropharmacological therapy demonstrated clinical improvement in patients with different types of cancer.[18] In addition, we demonstrated that the clinical improvement was paralleled by an increase in NK cell activity[7,19] These reports were further confirmed.[20-22] It was also demonstrated that clinical severity in cancer patients correlated negatively with NA/Ad ratio, whereas clinical improvement showed a positive correlation with NA/Ad. The forgoing findings are in line with those by other authors who demonstrated that some drugs able to improve colon and lung cancer, trigger NK cell activation.[22]

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